Paroxysmal Movement Disorder and Epilepsy Caused by a De Novo Truncating Mutation in *KAT6A*

Stephanie Efthymiou^{1,2} Vincenzo Salpietro¹ Conceicao Bettencourt^{1,2} Henry Houlden¹

¹Department of Molecular Neuroscience, Institute of Neurology, University College London, London, United Kingdom

²Department of Clinical and Experimental Epilepsy, Institute of Neurology, University College London, London, United Kingdom

Address for correspondence Henry Houlden, MD, PhD, Department of Molecular Neuroscience, Institute of Neurology, University College London, London WC1N 3BG, United Kingdom (e-mail: h.houlden@ucl.ac.uk).

J Pediatr Genet 2018;7:114–116.

Abstract

Keywords

- *KAT6A*
- startle reflex syndrome
- global developmental delay

Mutations in *KAT6A* encoding a histone acetyltransferase involved in chromatin remodeling and in other genes involved in histone acetylation and/or deacetylation have been implicated in broad phenotypes of congenital and developmental abnormalities. However, limited genotype–phenotype correlations are available for some of the most rare or recently reported genetic disorders related to chromatin dysregulation. We hereby report a de novo truncating mutation in *KAT6A* (c.3338C > G; p.S1113X) in a young male patient with intellectual disability associated with impaired speech and autistic features, who also presented with infantile seizures and a complex movement disorder phenotype with paroxysmal episodes of abnormal startle responses.

A 21-year-old man, born to unrelated healthy parents of French and Scottish descent (► **Fig. 1A**), presented since birth with hypotonia, feeding difficulties, and a small head circumference (31.75 cm; <3rd centile). Pregnancy and delivery were uncomplicated and there was no history of neurological disorders in the family, except for a maternal uncle who had epilepsy during his childhood. During the first months of life, a delay of developmental milestones was evident and he also had a history of focal and generalized infantile seizures, not associated with any recognizable trigger event, which spontaneously improved since the age of 3 years. Abnormal motor coordination and walking difficulties became evident in early infancy and progressed over time. At the current age of 21 years, the patient has no yet autonomous gait, and requires a walker or sometimes a wheelchair. Speech was absent in his childhood and he still has a nonverbal communication. As part of his neurological phenotype, he has exaggerated startle reflex syndrome, especially triggered by unexpected noises (► **Video 1**). These episodes usually last a few seconds with the patient experiencing generalized jerky movements that sometimes lead to sudden falls. The patient's paroxysmal episodes were not

accompanied by any electroencephalography ictal patterns, suggesting abnormal startle response rather than myoclonic seizures. Additionally, some distinctive facial features are also evident with a coarse face, dysplastic ears, prominent nasal bridge, prominent lower jaw, highly arched palate, and mild bitemporal narrowing (► **Fig. 1A**).

Video 1

The proband experiences repeated episodes of exaggerated startle response specifically in response to sudden or unexpected noise. Online content including video sequences viewable at: <https://www.thieme-connect.com/products/ejournals/html/doi/10-1055-s-0038-1651526-jpg-18-00010-v1.mp4>.

Repeated electroencephalography and brain magnetic resonance imaging studies performed during the follow-up were negative. Because of his complex clinical and neurological phenotype, he underwent several metabolic and

received

February 26, 2018

accepted

April 5, 2018

published online

June 14, 2018

Copyright © 2018 by Georg Thieme Verlag KG, Stuttgart · New York

DOI <https://doi.org/10.1055/s-0038-1651526>.
ISSN 2146-4596.

Fig. 1 (A) The pedigree diagram of the family. (B) The 21-year-old proband affected by exaggerated violent startle reflex syndrome due to a de novo *KAT6A* mutation. Note the distinctive facial features of prominent lower jaw and highly arched palate. (C) Individual results of Sanger sequencing showing the proband (II.1) carrying the de novo *KAT6A* truncating mutation (c.C3338G; p.S1113X) which is absent in both the parents (I.1, I.2). (D) A schematic illustration of the main functional domains of *KAT6A* protein: the nuclear localization domain (H15), a double-plaunt homeodomain finger (PHD), a histone-acetyl-transferase domain (HAT) containing a C2H2 zinc-finger domain (yellow), and an Acetyl-coenzyme-A-binding domain (red); an acidic glutamate/aspartate-rich domain and a transactivation domain with both a serine-rich (pink) and a methionine-rich (yellow) region. All previously reported *KAT6A* mutations indicated with arrows below, while our mutated de novo truncated version of *KAT6A* protein highlighted with the red cross and indicated with an arrow on the top.

genetic (including array comparative genome hybridization and panel sequencing of 55 genes causing intellectual disability) investigations that were all reported as normal. Thus, a trio-based whole exome sequencing (WES) was performed in the family (►Fig. 1A: I-1, I-2, II-1) as described elsewhere.¹ We identified a de novo heterozygous mutation in the *KAT6A* gene (c.3338C > G; p.S1113X, NM_006766) (►Fig. 1C).

We hereby describe a 21-year-old man with a complex clinical phenotype consisting of congenital microcephaly, hypotonia, global developmental delay, intellectual disability, seizures as an infant, absent speech, and a paroxysmal movement disorder consisting of exaggerated startle responses to sudden/unexpected noises. It is not clear if these are part of the underlying neurological disease or whether they represent functional (psychogenic) jerky movements, since we had not the opportunity to perform a neurophysiological evaluation to assess response and latency times.² To investigate the genetic cause of the disease in the proband, we performed WES and as part of our filtering strategy, only exonic and donor/acceptor splicing variants were considered. In accordance with the pedigree and phenotype, priority was given to rare variants (<0.01% in public databases, including 1,000 Genomes project, NHLBI Exome Variant Server, Complete Genomics 69, and Exome Aggregation Consortium [ExAC v0.2]) that were fitting a recessive (homozygous or compound heterozygous) or a de novo model and/or variants in genes previously linked to intellectual disability and neurological disorders. There were neither homozygous variants nor plausible compound heterozygous variants segregating with the disease in the family. We

also excluded other genes' variants that could be related to familial benign epilepsy and paroxysmal movement disorders (e.g., *PRRT2*). We identified a de novo nonsense variant in *KAT6A* (c.3338C > G; p.S1113X) as the most likely explanation for the disease pathogenesis. This is supported by a severe impact of the truncating mutation (►Fig. 1D) and existing reports of patients (*N* = 18) linking de novo nonsense mutations in this gene to a similar phenotype (MIM# 616268) with global developmental delay, intellectual disability, abnormal growth, and impaired (or absent) speech. In addition, 3 out of 18 had feeding difficulties, 6 had distinctive facial features, and 4 had congenital cardiac defects (i.e., 3 an atrial septal defect, 1 a ventricular septal defect).^{3–7} One of these cases had epilepsy that we observed in our patient, but none had the exaggerated startle responses.⁵

The *KAT6A* gene (MIM# 601408; also known as *MOZ* or *MYST3*) is abundantly expressed in the brain, with the highest levels during fetal development, and encodes a histone acetyltransferase (HAT) component of a multiprotein complex involved in several cellular processes (e.g., differentiation, metabolism, and apoptosis).^{5,8} The gene contains 18 exons and encodes a large 2004 amino acid protein, which includes a nuclear localization domain, a double C2H2 zinc finger domain that binds to acetylated histone tails, and a HAT domain (►Fig. 1D). Of interest, *KAT6A* knockout mouse models have been reported with severe abnormalities affecting the brain, gastrointestinal tract, and skeleton.⁹ Zebrafish genetic studies have also shown a crucial role of the chromatin remodeler gene *BRPF1* in regulating brain

development through *KAT6A*- and *KAT6B*-mediated H3K23 acetylation.⁸ Yan et al¹⁰ showed that nonsense mutations either in *KAT6A* or *KAT6B* cause deficiency of histone H3K23 acetylation, indicating a new emerging group of (clinically) overlapping developmental disorders due to abnormal histone H3 acetylation.

In conclusion, we confirmed epilepsy as a possible early infantile presentation within the *KAT6A*-associated neurological phenotype and also added paroxysmal startle response as a potential novel feature associated with the neurological spectrum of this syndrome. The future description of other patients carrying de novo *KAT6A* mutations will further expand the genotype–phenotype correlations in this rare and recently characterized genetic disorder.

Conflict of Interest

None.

Funding

This study was supported in part by The Wellcome Trust in equipment and strategic award (Synaptopathies) funding (WT093205 MA and WT104033AIA).

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Author Contributions

Stephanie Efthymiou: study design and experimental data acquisition, analysis and interpretation of data.

Dr. Vincenzo Salpietro: study concept and clinical data contribution to the manuscript, analysis and interpretation of data.

Dr. Conceicao Bettencourt: critical revision of the manuscript document.

Prof. Henry Houlden: study supervision.

Acknowledgments

We gratefully acknowledge the family for the enthusiastic collaboration to this study.

References

- 1 Mencacci NE, Kamsteeg EJ, Nakashima K, et al. De novo mutations in PDE10A cause childhood-onset chorea with bilateral striatal lesions. *Am J Hum Genet* 2016;98(04):763–771
- 2 Dreissen YEM, Boeree T, Koelman JHTM, Tijssen MAJ. Startle responses in functional jerky movement disorders are increased but have a normal pattern. *Parkinsonism Relat Disord* 2017; 40:27–32
- 3 Tham E, Lindstrand A, Santani A, et al. Dominant mutations in *KAT6A* cause intellectual disability with recognizable syndromic features. *Am J Hum Genet* 2015;96(03):507–513
- 4 Murray CR, Abel SN, McClure MB, et al. Novel causative variants in *DYRK1A*, *KARS*, and *KAT6A* associated with intellectual disability and additional phenotypic features. *J Pediatr Genet* 2017;6(02): 77–83
- 5 Millan F, Cho MT, Retterer K, et al. Whole exome sequencing reveals de novo pathogenic variants in *KAT6A* as a cause of a neurodevelopmental disorder. *Am J Med Genet A* 2016;170(07): 1791–1798
- 6 Arboleda VA, Lee H, Dorrani N, et al; UCLA Clinical Genomics Center. De novo nonsense mutations in *KAT6A*, a lysine acetyl-transferase gene, cause a syndrome including microcephaly and global developmental delay. *Am J Hum Genet* 2015;96(03):498–506
- 7 Zwaveling-Soonawala N, Alders M, Jongejan A, et al. Clues for polygenic inheritance of pituitary stalk interruption syndrome from exome sequencing in 20 patients. *J Clin Endocrinol Metab* 2018;103(02):415–428
- 8 Good-Jacobson KL, Chen Y, Voss AK, Smyth GK, Thomas T, Tarlinton D. Regulation of germinal center responses and B-cell memory by the chromatin modifier MOZ. *Proc Natl Acad Sci U S A* 2014;111(26):9585–9590
- 9 Voss AK, Vanyai HK, Collin C, et al. MOZ regulates the Tbx1 locus, and Moz mutation partially phenocopies DiGeorge syndrome. *Dev Cell* 2012;23(03):652–663
- 10 Yan K, Rousseau J, Littlejohn RO, et al; DDD Study; CAUSES Study. Mutations in the chromatin regulator gene *BRPF1* cause syndromic intellectual disability and deficient histone acetylation. *Am J Hum Genet* 2017;100(01):91–104